Exhibit "F"

Article 2

NEUROLOGY

The minimally conscious state: Definition and diagnostic criteria

J.T. Giacino, S. Ashwal, N. Childs, R. Cranford, B. Jennett, D.I. Katz, J.P. Kelly, J.H. Rosenberg, J. Whyte, R.D. Zafonte and N.D. Zasler

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Special Article

CME

The minimally conscious state

Definition and diagnostic criteria

J.T. Giacino, PhD; S. Ashwal, MD; N. Childs, MD; R. Cranford, MD; B. Jennett, MD; D.I. Katz, MD; J.P. Kelly, MD; J.H. Rosenberg, MD; J. Whyte, MD, PhD; R.D. Zafonte, DO; and N.D. Zasler, MD

Abstract—*Objective:* To establish consensus recommendations among health care specialties for defining and establishing diagnostic criteria for the minimally conscious state (MCS). *Background:* There is a subgroup of patients with severe alteration in consciousness who do not meet diagnostic criteria for coma or the vegetative state (VS). These patients demonstrate inconsistent but discernible evidence of consciousness. It is important to distinguish patients in MCS from those in coma and VS because preliminary findings suggest that there are meaningful differences in outcome. *Methods:* An evidence-based literature review of disorders of consciousness was completed to define MCS, develop diagnostic criteria for entry into MCS, and identify markers for emergence to higher levels of cognitive function. *Results:* There were insufficient data to establish evidence-based guidelines for diagnosis, prognosis, and management of MCS. Therefore, a consensus-based case definition with behaviorally referenced diagnostic criteria was formulated to facilitate future empirical investigation. *Conclusions:* MCS is characterized by inconsistent but clearly discernible behavioral evidence of consciousness and can be distinguished from coma and VS by documenting the presence of specific behavioral features not found in either of these conditions. Patients may evolve to MCS from coma or VS after acute brain injury. MCS may also result from degenerative or congenital nervous system disorders. This condition is often transient but may also exist as a permanent outcome. Defining MCS should promote further research on its epidemiology, neuropathology, natural history, and management.

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Precise estimates of the incidence and prevalence of severe disorders of consciousness are unavailable. In the United States, the number of individuals who sustain severe traumatic brain injury (i.e., brain injury caused by externally inflicted trauma[1]) with prolonged loss of consciousness each year is estimated to be between 56 and 170 per one million.[2,3] The economic impact of the problem is enormous. Projected average per person lifetime costs of care alone for severe traumatic brain injury range from $600,000 to $1,875,000.[4] A single case described by Paris[5] reported in-hospital lifetime costs of $6,104,590. In the last 5 years, there have been some attempts to clarify and define diagnostic, prognostic, and treatment issues concerning patients with severe disturbances of consciousness.[6-10] Disorders of consciousness include coma and the vegetative state (VS). Patients in coma have complete failure of the arousal system with no spontaneous eye opening and are unable to be awakened by application of vigorous sensory stimulation.[11] VS is characterized by the complete absence of behavioral evidence for self or environmental awareness. There is preserved capacity for spontaneous or stimulus-induced arousal, evidenced by sleep–wake cycles.[12] The locked-in syndrome, characterized by anarthria and quadriplegia with general preservation of cognition, must be distinguished from disorders of consciousness.[11] The table outlines the clinical features of disorders of consciousness and the locked-in syndrome.

Some patients with severe alteration in consciousness have neurologic findings that do not meet criteria for VS. These patients demonstrate discernible

See also pages 337 and 506

The American Academy of Neurology has reviewed this document and recommends it to Academy membership as an educational tool. This document has been endorsed by the American Academy of Physical Medicine and Rehabilitation, the American Association of Neurological Surgeons, the American Congress of Rehabilitation Medicine, the Brain Injury Association, Inc., and the Child Neurology Society.

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Table Comparison of clinical features associated with coma, vegetative state, minimally conscious state, and locked-in syndrome

Condition	Consciousness	Sleep/wake	Motor function	Auditory function	Visual function	Communication	Emotion
Coma	None	Absent	Reflex and postural responses only	None	None	None	None
Vegetative state	None	Present	Postures or withdraws to noxious stimuli	Startle	Startle	None	None
			Occasional nonpurposeful movement	Brief orienting to sound	Brief visual fixation		Reflexive crying or smiling
Minimally conscious state	Partial	Present	Localizes noxious stimuli	Localizes sound location	Sustained visual fixation	Contingent vocalization	Contingent smiling or crying
			Reaches for objects	Inconsistent command following	Sustained visual pursuit	Inconsistent but intelligible verbalization or gesture	
			Holds or touches objects in a manner that accommodates size and shape				
			Automatic movements (e.g., scratching)				
Locked-in syndrome	Full	Present	Quadriplegic	Preserved	Preserved	Aphonic/Anarthric	Preserved
						Vertical eye movement and blinking usually intact	

behavioral evidence of consciousness but remain unable to reproduce this behavior consistently. This condition is referred to here as the minimally conscious state (MCS). MCS is distinguished from VS by the partial preservation of conscious awareness.[13] This distinction is important for prognosis, treatment decisions, resource allocation, and medicolegal judgements. Some studies suggest a high rate of misdiagnosis (false positives and false negatives) among disorders of consciousness.[14,15] The prevalence of adult and pediatric cases of MCS is estimated to be between 112,000 to 280,000, based on operationally defined diagnostic criteria extracted from a large state registry.[16]

This article, prepared by the Aspen Neurobehavioral Conference Workgroup, proposes diagnostic criteria for MCS.

Methods. *Evidence review process.* Nine formal meetings of the Aspen Workgroup were held between March 1995 and October 2000. National and international delegates represented the fields of bioethics, neurology, neuropsychology, neurosurgery, physiatry, nursing, and allied health. Although it was not possible for each participant to attend all nine meetings, the current document was approved by all members of the workgroup. All delegates previously participated in the development of discipline-specific position statements on disorders of consciousness or made substantial contributions to the peer-reviewed literature. A list of the organizations represented by each author appears in the appendix, which also includes the names of all conference participants.

Selected members of the workgroup completed independent MEDLINE searches of published articles using the key words coma, vegetative state, minimally responsive state, stupor, slow-to-recover, severe disability, and Glasgow Coma Scale. These terms were then cross-indexed with brain injury, diagnosis, and outcome in eight different permutations to retrieve articles that included patients who did not meet diagnostic criteria for VS, but at the same time, were not considered fully conscious. A total of 260 abstracts containing one or more of the terms were retrieved. Only five reports[8,17-20] differentiated patients in VS from those with inconsistent signs of consciousness, defined here as MCS. The workgroup concluded that there were insufficient data to establish evidence-based guidelines for diagnosis, prognosis, and management of MCS. Consequently, consensus-based recommendations were developed for the definition of MCS as well as criteria for entry into and emergence from this condition.

Results. *Definition of the minimally conscious state.* The minimally conscious state is a condition of severely altered consciousness in which minimal but definite behav-

ioral evidence of self or environmental awareness is demonstrated.

Diagnostic criteria for the minimally conscious state. MCS is distinguished from VS by the presence of behaviors associated with conscious awareness. In MCS, cognitively mediated behavior occurs inconsistently, but is reproducible or sustained long enough to be differentiated from reflexive behavior. The reproducibility of such evidence is affected by the consistency and complexity of the behavioral response. Extended assessment may be required to determine whether a simple response (e.g., a finger movement or eye blink) that is observed infrequently is occurring in response to a specific environmental event (e.g., command to move fingers or blink eyes) or on a coincidental basis. In contrast, a few observations of a complex response (e.g., intelligible verbalization) may be sufficient to determine the presence of consciousness.

To make the diagnosis of MCS, limited but clearly discernible evidence of self or environmental awareness must be demonstrated on a reproducible or sustained basis by one or more of the following behaviors:

- Following simple commands.
- Gestural or verbal yes/no responses (regardless of accuracy).
- Intelligible verbalization.
- Purposeful behavior, including movements or affective behaviors that occur in contingent relation to relevant environmental stimuli and are not due to reflexive activity. Some examples of qualifying purposeful behavior include:
  - appropriate smiling or crying in response to the linguistic or visual content of emotional but not to neutral topics or stimuli
  - vocalizations or gestures that occur in direct response to the linguistic content of questions
  - reaching for objects that demonstrates a clear relationship between object location and direction of reach
  - touching or holding objects in a manner that accommodates the size and shape of the object
  - pursuit eye movement or sustained fixation that occurs in direct response to moving or salient stimuli

Although it is not uncommon for individuals in MCS to demonstrate more than one of the above criteria, in some patients the evidence is limited to only one behavior that is indicative of consciousness. Clinical judgments concerning a patient's level of consciousness depend on inferences drawn from observed behavior. Thus, sensory deficits, motor dysfunction, or diminished drive may result in underestimation of cognitive capacity.

Proposed criteria for emergence from the minimally conscious state. Recovery from MCS to higher states of consciousness occurs along a continuum in which the upper boundary is necessarily arbitrary. Consequently, the diagnostic criteria for emergence from MCS are based on broad classes of functionally useful behaviors that are typically observed as such patients recover. Thus, emergence from MCS is characterized by reliable and consistent demonstration of one or both of the following:

- Functional interactive communication.
- Functional use of two different objects.

Functional interactive communication may occur through verbalization, writing, yes/no signals, or use of augmentative communication devices. Functional use of objects requires that the patient demonstrate behavioral evidence of object discrimination.

To facilitate consistent reporting of findings among clinicians and investigators working with patients in MCS, the following parameters for demonstrating response reliability and consistency should be used:

- Functional communication: accurate yes/no responses to six of six basic situational orientation questions on two consecutive evaluations. Situational orientation questions include items such as, "Are you sitting down?" and "Am I pointing to the ceiling?"
- Functional object use: generally appropriate use of at least two different objects on two consecutive evaluations. This criterion may be satisfied by behaviors such as bringing a comb to the head or a pencil to a sheet of paper.

To help ensure that the operational parameters for demonstrating functional communication and object use described above are equivalent in terms of difficulty, the neurobehavioral profiles of a convenience sample of patients in MCS ($n = 24$) extracted from a database maintained by one of the authors were reviewed (unpublished data). From this pool, 17 patients were identified who met criteria for either functional object use (FO) or functional communication (FC). The temporal course of recovery of FO and FC was investigated to determine whether the sequence of recovery could serve as an index of difficulty. For example, if most patients met criteria for FO before the criteria for FC were satisfied, it could be concluded that the criteria for FC were more stringent. Data were analyzed for 15 of the 17 available patients. Two patients were excluded because both FO and FC were intact on the admitting examination. Among the remaining 15 patients, seven recovered FO before FC; three recovered FC before FO; and five recovered FO and FC concurrently. The mean time between recovery of FO and FC (independent of sequence) was 8 days (range, 5 to 14 days). Based on these findings, it was concluded that the operational criteria for FO and FC are of equal difficulty.

It is necessary to exclude aphasia, agnosia, apraxia, or sensorimotor impairment as the basis for nonresponsiveness, as opposed to diminished level of consciousness. As noted previously, the criteria for emergence from MCS may underestimate the level of consciousness in some patients. For example, patients with some forms of akinetic mutism demonstrate limited behavioral initiation but are capable of occasional complex cognitively mediated behavior. When there is evidence to suggest that the assessment of level of consciousness is confounded by diminished behavioral initiation, further diagnostic investigation is indicated. Until these diagnostic ambiguities can be resolved by future research, the above definitions should be applied to all patients whose behavior fails to substantiate higher levels of consciousness. It is likely that studies investigating the neurologic substrate underlying subgroups of MCS patients will, in the future, allow the development of diagnostic criteria that are more reliably tied to the level of consciousness.

Recommendations for behavioral assessment of neurocognitive responsiveness. Differential diagnosis among states of impaired consciousness is often difficult. The following steps should be taken to detect conscious awareness and to establish an accurate diagnosis:

1. Adequate stimulation should be administered to ensure that arousal level is maximized.
2. Factors adversely affecting arousal should be addressed (e.g., sedating medications and occurrence of seizures).
3. Attempts to elicit behavioral responses through verbal instruction should not involve behaviors that frequently occur on a reflexive basis.
4. Command-following trials should incorporate motor behaviors that are within the patient's capability.
5. A variety of different behavioral responses should be investigated using a broad range of eliciting stimuli.
6. Examination procedures should be conducted in a distraction-free environment.
7. Serial reassessment incorporating systematic observation and reliable measurement strategies should be used to confirm the validity of the initial assessment. Specialized tools and procedures designed for quantitative assessment may be useful.[17,19,21-25]
8. Observations of family members, caregivers, and professional staff participating in daily care should be considered in designing assessment procedures.

Special care must be taken when evaluating infants and children younger than 3 years of age who have sustained severe brain injury. In this age group, assessment of cognitive function is constrained by immature language and motor development. This limits the degree to which command following, verbal expression, and purposeful movement can be relied on to determine whether the diagnostic criteria for MCS have been met.

Prognosis. The natural history and long-term outcome of MCS have not yet been adequately investigated. It is essential to recognize that MCS may occur in a variety of neurologic conditions, such as traumatic brain injury, stroke, progressive degenerative disorders, tumors, neurometabolic diseases, and congenital or developmental disorders. Clinical experience indicates that MCS after an acute injury can exist as a transitional or permanent state. Few studies of the natural history of MCS have been reported.[22,26,27] Giacino and Kalmar[22] followed 104 patients diagnosed with VS (n = 55) or MCS (n = 49) on admission to rehabilitation during the first 12 months after injury. The diagnosis of MCS was made retrospectively using clinical criteria that approximate the current definition. The MCS group showed more continuous improvement and attained significantly more favorable outcomes on the Disability Rating Scale[28] by 1 year than did the VS group. These differences were more pronounced in patients diagnosed with MCS after traumatic brain injury. Fifty percent of patients in the MCS group with traumatic brain injury were found to have none to moderate disability at 12 months, whereas none of the patients in the MCS group without traumatic brain injury were classified in these outcome categories. Although it is not known how many patients will emerge from MCS after 12 months after injury, most patients in MCS for this length of time remain severely disabled according to the Glasgow Outcome Scale.[29] As with VS, the likelihood of significant functional improvement diminishes over time.

Consensus-based general approaches to care. There are no existing guidelines regarding the care of patients in MCS. Until sufficient empirical data become available, the following general consensus-based approaches to care are recommended. Evaluation and management decisions will differ depending on the prognosis and the needs of the patient. In all circumstances, the patient should be treated with dignity, and caregivers should be cognizant of the patient's potential for understanding and perception of pain. In early MCS, prevention of complications and maintenance of bodily integrity should be emphasized because of the likelihood of further improvement. Efforts should be made to establish functional communication and environmental interaction when possible. A person with experience in neurologic assessment of patients with impaired consciousness should be primarily responsible for establishing the diagnosis and prognosis and for coordinating clinical management. An additional opinion of a physician or other professional with particular expertise in the evaluation, diagnosis, and prognosis of patients in VS and MCS is recommended when the assessment will impact critical management decisions. Such decisions include, but are not limited to, those regarding changes in level of care, disputed treatment decisions, and withdrawal of life-sustaining treatment.

Future directions for research. The care of patients with severe disturbances of consciousness remains a complex challenge partly because of an inadequate foundation of scientific evidence. There are a number of critical areas in which scientific evidence is lacking and additional research is indicated. These areas include:

1. Incidence and prevalence of MCS.
2. Natural history, recovery course, and outcome.
3. Interrater and test–retest reliability of the diagnostic criteria for MCS.
4. Validation of diagnostic criteria for MCS with respect to pathophysiologic mechanisms and outcome.
5. Differences in rate of recovery and outcome between adults and children.
6. Interactions among cause of the injury (e.g., trauma vs anoxia vs dementia), length of time after onset, and recovery of consciousness.
7. Predictors and patterns of emergence from VS and MCS.
8. Utility of existing assessment methods and scales for monitoring recovery and predicting outcome.
9. Treatment efficacy.
10. Efficacy and cost analysis of different care settings.
11. Issues related to family beliefs and their relation to functional outcome, service use, and evaluative decisions regarding quality of life.
12. Cross-cultural differences in evaluation and management practices.

These recommendations are intended to serve as a reference for clinicians involved in the examination and treatment of patients with severe alterations in consciousness. They are based on the current state of knowledge and are expected to be revised and refined as additional empirical data become available. The primary purpose of these recommendations is to facilitate future scientific investigation and multidisciplinary discussion by providing a common frame of reference for the examination and treatment of patients in MCS.

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AMERICAN ACADEMY OF NEUROLOGY

Article 3

EDITORIAL REVIEW

What is it like to be vegetative or minimally conscious?

Steven Laureys and Melanie Boly

Purpose of review

Patients in a vegetative or minimally conscious state continue to pose problems in terms of diagnosis, prognosis and treatment. Despite recent waves of international media attention following Terri Schiavo's death and the 'miracle recovery' of Terry Wallis, research efforts aimed at increasing our knowledge about brain function in these conditions remain scarce and must address a series of difficulties, including financial and ethical barriers. Here we review current possibilities and limitations of clinical and para-clinical assessment of chronic disorders of consciousness.

Recent findings

During the past year the field has witnessed publication of significant, yet isolated, case reports in top ranking journals, including *Science* and *Nature*. Such milestone reports and other impressive recent technological advances in the study of vegetative and minimally conscious patients reveal enthralling areas of science that must find their way to clinical medical reality.

Summary

Consciousness is a subjective experience whose study has remained within the purview of philosophy for millennia. That has finally changed, and empirical evidence from functional neuroimaging offers a genuine glimpse at a solution to the infamous mind–body conundrum. New technological and scientific advances offer the neurological community unique ways to improve our understanding and management of vegetative and minimally conscious patients.

Keywords

consciousness, ethics, functional magnetic resonance imaging, minimally conscious state, vegetative state

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Abbreviations

DBS	deep brain stimulation
DOC	disorder of consciousness
MRI	magnetic resonance imaging
MCS	minimally conscious state

1350-7540

Introduction

About 50 years ago, before the era of neurocritical care, things were relatively simple. Following severe brain damage, comatose patients either died or, more rarely, recovered with cerebral deficit of varying severity. The invention of the positive pressure mechanical ventilator by Bjorn Ibsen in the 1950s in Copenhagen and the development of intensive care in the 1960s in the industrialized world have meant that heart function and systemic circulation can be sustained by artificial respiratory support in patients suffering traumatic and nontraumatic brain damage. The resulting profound unconscious states had never previously been encountered, because until that time all such patients had died instantly from apnoea. This change forced the medical community to redefine death, leading to its neurological definition: brain death (i.e. irreversible coma with absent brainstem reflexes) [1].

In the 1960s Fred Plum and Jerome Posner from New York first described the rare but terrifying situation of comatose patients recovering consciousness but remaining unable to move or speak, classically communicating only via eye movements. In their milestone book 'The diagnosis of stupor and coma' [2], they termed this condition the 'locked-in syndrome'. In 1972 Bryan Jennett from Glasgow and Fred Plum reported in the *Lancet* the clinical criteria for another artefact of modern intensive care: the vegetative state [3]. Patients in a vegetative state awaken from their coma (i.e. they open their eyes) but remain unaware (i.e. they exhibit solely reflex behaviour). Hence, until very recently patients surviving severe brain damage were considered to be comatose, vegetative or conscious. In 2002, the Aspen Neurobehavioral Conference Workgroup recognized that the clinical reality was even more complicated and that some patients showed signs of voluntary behaviour (and hence could not be considered vegetative) but remained unable to communicate functionally. The Workgroup reported diagnostic criteria for a new clinical entity: the minimally conscious state (MCS) [4].

Treating patients with an acute or chronic disorder of consciousness (DOC) remains challenging. The debate on the need to continue or to stop 'futile' treatment in hopeless acute comatose states was begun in the 1970s, and the need to withhold/withdraw treatment in desperate cases is now widely accepted in intensive care [5]. Today, almost half of all deaths in critical care units follow a decision to withhold or withdraw therapy [6]. Since the 1994 meta-analysis conducted by the Multi-Society Task Force on Persistent Vegetative State was published [7], we have learned that the chances of recovery from a chronic vegetative state are close to zero 1 year after traumatic and 3 months after nontraumatic brain damage. In these cases of permanent vegetative state, treatment can be considered futile and its withdrawal can be ethically justified, based on the principles of patient autonomy, beneficence and nonmaleficence. Outcomes in MCS patients are considered to be better, and at present no time intervals for possible permanency of the condition have been established. No generally accepted standards of care have been proposed for patients in MCS.

How should we best care for these patients with a chronic DOC? Can withholding or withdrawal of treatment be justified in some cases? It is generally accepted that competent patients should consent to any treatment that they receive and have the right to make choices regarding their bodies and lives. The primary factor determining the level of treatment for an incompetent patient should reflect that patient's personally expressed wishes in their situation. By definition, however, patients in vegetative state or MCS cannot communicate their wishes.

What is it like to be unconscious or minimally conscious? Can patients with DOCs experience suffering or satisfaction? What is their quality of life? Is the level and content of consciousness in these patients with such severely damaged brains in any way comparable to our own? These questions are difficult to answer. The philosopher Thomas Nagel, author of the landmark paper 'What is it like to be a bat?' [8], might even argue that the subjective aspect of the mind will never be sufficiently accounted for by the objective methods of reductionistic science. We prefer a more pragmatic approach and believe that scientific and technological advances will ultimately improve our understanding and management of patients suffering from severe DOCs.

To be or not be ... vegetative

Good medical management begins by making a correct diagnosis. There is an irreducible limitation in knowing for certain whether any other being is conscious [9]. Vegetative patients can move extensively, and clinical studies (for review, see Majerus *et al.* [10]) have shown how difficult it is to differentiate reflex or 'automatic' from voluntary or 'willed' movements [11]. This results in an underestimation of behavioural signs of consciousness and hence misdiagnosis, which is estimated to occur in about one-third to nearly half of chronically vegetative patients [12,13]. In this issue, Giacino and Smart (pp. 614–619), from the New Jersey Neuroscience Institute and JFK Johnson Rehabilitation Institute, discuss the crucial role played by adapted behavioural assessment tools in the diagnostic work-up of DOC. Differentiating vegetative from minimally conscious patients requires expertise, experience and effort. Clinical testing for the absence of consciousness in vegetative state is much more problematic and slippery than testing for absence of wakefulness in coma. Vegetative state is one end of a spectrum of awareness, and the subtle differential diagnosis with MCS necessitates repeated evaluations by skilled examiners employing standardized rating scales such as the Coma Recovery Scale-Revised, developed by Giacino *et al.* [14]. Diagnostic error may in part be accounted for by the fact that signs of consciousness in these patients often are subtle and fluctuating. Other causes could be related to limited examination skills and lack of knowledge of diagnostic criteria.

Giacino and Smart also point to international differences in diagnostic criteria for vegetative state. They argue that the vegetative state patient exhibiting brain activation indicative of mental imagery of 'tennis playing', reported last year in *Science* by the Cambridge and Liège coma groups [15], would have been diagnosed as MCS according to US guidelines, given that the reported patient showed visual fixation. Visual fixation is one of the more controversial clinical signs of consciousness. The 2003 UK Royal College of Physicians Guidelines [16] considered fixation as a 'compatible but atypical feature', whereas the 2002 US Aspen Workgroup [4] criteria regard sustained (but not brief) fixation as a purposeful movement and hence as a sufficient sign of MCS. There are no guidelines specifying what time interval differentiates a sustained from a brief visual fixation. Other controversial clinical signs are the definition and clinical assessment of visual tracking, blinking in response to visual threat, and orientated motor responses to noxious stimuli. It is clear that international consensus on nosological criteria is a prerequisite for establishing evidence-based medicine in our field.

Do they suffer?

Schnakers from the Coma Science Group of Liège and Zasler from the Concussion Care Centre of Virginia (pp. 620–626) examine current knowledge to inform decisions regarding the management of pain in DOCs. Like consciousness, pain is a subjective experience. By definition, patients in vegetative state and MCS cannot communicate their feelings and possible pain perception. The behavioural assessment of motor or autonomic signs

(i.e. heart rate, respiratory frequency, blood pressure, pupillary diameter and skin conductance) have been demonstrated not to be reliable indicators of conscious perception of pain (e.g. see studies done in general anaesthesia [17]).

Only two positron emission tomography studies have studied brain processing linked to pain in vegetative state and the findings were contradictory. Laureys *et al.* [18] compared cerebral activation by high-intensity electrical stimulation of the median nerve at the wrist between 15 vegetative state patients (12 nontraumatic, mean post-insult time 1 month) and 15 healthy volunteers. The results demonstrated preserved and robust activation of the brainstem, thalamus and primary somatosensory cortex in every patient. However, this residual activation was like an island, disconnected from the rest of the 'pain matrix' (including the anterior cingulate cortex, which is considered critical in the affective and cognitive processing of pain) and the higher order cortical network that is considered necessary for conscious processing. Kassubek *et al.* [19] used similar methodology in seven vegetative state patients (all anoxic, mean post-insult time 1.5 years) and confirmed activation in primary somatosensory cortex but also – and surprisingly – in secondary somatosensory, insular and anterior cingulate cortices.

Schnakers and Zasler, considering the current levels of clinical and scientific uncertainty, propose that pain treatment be given to all patients in vegetative state or MCS. Current clinical guidelines do not share this view and do not propose the use of analgesics in vegetative state [7] (e.g. Terri Schiavo died without administration of therapeutic doses of opiates). The pros and cons of the use of analgesia in those who are severely brain damaged, and are unable to communicate possible perception of pain, are complex. Systematic use of narcotic analgesics in DOCs could lead to undesired sedation and subsequent underestimation of signs of consciousness. On the contrary, some patients might experience hyperalgesia, requiring more aggressive analgesic therapy. As concluded by Schnakers and Zasler, much more research is needed to develop scientifically based guidelines. Such research, however, faces major ethical challenges. For some scholars noxious stimuli cannot be applied to patients who are unable to provide written informed consent. In DOCs exploration of behavioural responses to nociceptive stimuli (e.g. applying pressure to the fingernail bed with a pencil, applying pressure to the supraorbital ridge or jaw angle, pinching the trapezium, or rubbing the sternum) is a routine clinical procedure that is used to evaluate the state of consciousness. Reactivity to pain is part of widely used 'consciousness scales', such as the Glasgow Coma Scale.

Caring for severely brain damaged patients represents such an immense humane, affective and social problem that it warrants further research to understand better the underlying cerebral dysfunction of vegetative state and MCS. Excluding the study of possible residual perception of pain from research protocols would in our view not be ethically justifiable. Fins (pp. 650–654) from Cornell University in New York discusses the need for an ethical framework based on prudential ethic with respect to dissemination of new scientific methodology and technology, distinguishing investigational from clinical efforts and complementing neuroimaging studies with longitudinal epidemiological inquiry into the natural history of DOCs. His eloquent essay addresses the ethical implications of recent technological developments for public policy, emerging therapeutics, and diagnostic and prognostic assessment in these challenging patient populations.

Hope from functional neuroimaging

At present, we still do not have validated prognostic markers that allow us to predict the chances of recovery in the individual patient in vegetative state or MCS. Galanaud, Naccache and Puybasset (pp. 627–631) from Pitié Salpêtrière Hospital in Paris discuss the predictive value of advanced magnetic resonance imaging (MRI) methods such as voxel-based volumetry or morphometry (i.e. objective quantification of changes in brain structure), magnetic resonance spectroscopy [i.e. measurement of metabolites such as *N*-acetyl-aspartate (a biomarker for neuronal integrity), choline (a marker for cell membrane turnover) and creatine (for cellular energetic function)] and MRI diffusion tensor imaging (i.e. assessment of the density, integrity and directionality of white matter tracts) in coma and related conditions. The reviewed evidence is still sparse and preliminary, and requires confirmation from ongoing large-scale multicentre studies. We hope that in the near future early para-clinical prognostic markers will allow us to identify irreversibility in vegetative patients, similar to current markers of irreversibility in coma such as electroencephalography (absent or burst-suppression electrical activity) and somatosensory evoked potentials (absence of N20 responses).

Positron emission tomography and functional MRI studies have not yet been shown to be reliable markers of recovery of consciousness. They have allowed us to reject the ancient view that vegetative patients are neocortically dead or apallic [20]. A succession of neuroimaging data has shown cerebral activation in isolated and disconnected islands of 'lower level' cortices or 'pallium' in response to auditory, visual, somatosensory and noxious stimuli [21]. Functional neuroimaging studies (e.g. see the reports by Boly and coworkers [22,23]) have also provided scientific evidence that residual brain function in vegetative state is very different from the brain's integrative capacity in MCS. These studies have confirmed that vegetative state and MCS are truly different physiological entities [24].

Owen and Coleman (pp. 632–637) from Cambridge review their hierarchical functional MRI approach to assessing language perception in DOC, beginning with basic acoustic processing and progressively going on to more complex aspects of cognition. Although it is very powerful and informative, the limitation of this approach is that – in the absence of a full understanding of the neural correlates of consciousness – even a normal activation in response to passive sensory stimulation cannot be taken as incontestable proof of consciousness. In contrast, repeated and prolonged activation in response to an instruction to perform a mental imagery task would provide undeniable evidence of voluntary task-dependent brain activity, and hence of consciousness. This ground-breaking approach was validated by Boly *et al.* [25] in healthy control individuals, and it has been successfully applied to identify conscious perception in a (thus far unique) patient behaviourally diagnosed as being in a post-traumatic vegetative state, studied by Owen *et al.* [15].

Thought stimulation and thought translation devices

Therapeutic options in vegetative state and MCS are limited, and at present there is no pharmacological or nonpharmacological treatment proven to be efficient in DOCs. Moruzzi and Magoun's pioneering work in the 1940s demonstrated the critical role played by the brainstem and thalamic reticular system in higher brain activation [26]. Since the 1970s, multiple attempts have been made to use electrical stimulation of the tegmental midbrain, nonspecific thalamic nuclei and globus pallidus to improve arousal and awareness in patients in vegetative state. During the 1980s, a large multicentre study enrolled patients in France, Japan and the USA (its most famous patient being Terri Schiavo). However, none of these trials employing deep brain stimulation (DBS) in vegetative state yielded convincing results. In 2000, a report published in the *Lancet* [27] showed that restoration of functional disconnections between intralaminar thalamus and frontal cortices paralleled recovery of consciousness from vegetative state. This year, a well documented chronic post-traumatic MCS patient, carefully selected by means of functional neuroimaging, demonstrated unequivocal behavioural improvements related to intralaminar thalamic DBS [28]. Schiff and Fins (pp. 638–642 and 650–654) from Cornell University in New York consider their and other DBS cases within a historical context and examine the challenges for further clinical development of the technique.

Brain computer interfaces or thought translation devices permit communication via voluntary electroencephalography control, without any motor involvement. Technological improvements in such devices have now enabled locked-in patients to control their surroundings in ways that were not possible previously [29]. Andrea Kübler and Boris Kotchoubey (pp. 643–649) from the University of Tübingen discuss the role of brain computer interfaces not only as a communication instrument in locked-in syndrome but also as a diagnostic tool in DOCs. It is thrilling to witness the use of this powerful approach in the assessment of possible residual consciousness in patients clinically diagnosed as 'vegetative state' or 'MCS'.

Conclusion

The question of what it feels like to be minimally conscious has not yet been resolved, but the technology at least to attempt to address this issue now exists. Severe brain damage represents an immense social and economic problem that warrants further research. Unconscious, minimally conscious and locked-in patients are vulnerable and deserve special procedural protection, but they are also vulnerable to being denied proper care if the medical community does not increase its research efforts.

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Article 5

POSITION PAPER

Recommendations for Use of Uniform Nomenclature Pertinent to Patients With Severe Alterations in Consciousness

American Congress of Rehabilitation Medicine

ABSTRACT. American Congress of Rehabilitation Medicine. Recommendations for use of uniform nomenclature pertinent to patients with severe alterations in consciousness. Position paper. Arch Phys Med Rehabil 1995;76: 205-9.

• There continues to be considerable confusion and controversy on the use of diagnostic and clinical terms assigned to patients with severe alterations in consciousness. This confusion results largely from the lack of a uniform classification system that is based on behaviorally defined criteria. This position paper provides recommendations for defining coma, vegetative state (including *persistent* and *permanent* vegetative state), akinetic mutism, the minimally responsive state, and locked-in syndrome based on neurobehavioral and neuropathologic features. Current controversies surrounding use of these terms also are discussed.

Each year, the number of survivors of severe brain injury increases. Improvements in critical care management and rehabilitative treatment are primarily responsible for the decrease in mortality rates that has occurred in the last 15 years. Although many of these survivors will achieve significant recovery of function, as many as 30% to 40% will remain in prolonged states of severely reduced consciousness subsequent to achieving medical stability.[1]

Few rehabilitation specialists would argue the importance of establishing an accurate diagnosis after severe neurologic injury, yet broad disagreement and confusion continues on the use of diagnostic terms applied to this population. Terms most commonly used include "coma," "vegetative state (VS)," and "persistent vegetative state (PVS)." The problem of misdiagnosis is illustrated in a recent study by Childs et al,[2] who found a high rate of diagnostic inaccuracy in a group of patients admitted to an inpatient rehabilitation center. These investigators found that 37% of patients admitted with diagnoses of coma or PVS were diagnosed incorrectly according to American Medical Association criteria.[3] Misdiagnosis was judged on the basis of behavioral evidence of cognitive responsiveness (eg, command following, visual pursuit). Interestingly, the rate of misdiagnosis was significantly higher for traumatic versus nontraumatic injuries. Childs and associates concluded that the diagnostic inaccuracy noted in their study was attributable to confusion in the terms used in the literature to describe alterations in states of consciousness, nonuniform use of existing classification systems, and lack of extended observation. These findings are particularly alarming because the problem of diagnostic inaccuracy in this population was identified more than 10 years ago[4] and does not appear to have changed significantly since then.

PURPOSE

The ongoing problems with diagnostic accuracy and specificity, coupled with the potential for misdiagnosis to lead to inappropriate treatment recommendations, led the Committee on the Minimally Responsive Patient of the American Congress of Rehabilitation Medicine—Head Injury Interdisciplinary Special Interest Group to attempt to define diagnostic nomenclature pertinent to this population. The goals were to develop definitions with the following criteria: (1) could be universally applied, ie, across disciplines, across centers; (2) were based on behavioral response characteristics; and (3) would yield high interrater reliability rates.

This document provides recommendations for definitions of six terms that have been studied by the committee for the past 4 years. The terms were chosen based on informal estimates of frequency of use and degree of perceived confusion regarding their respective clinical criteria. The following terms were chosen: (1) "coma"; (2) "vegetative state (VS)"; (3) "persistent vegetative state (PVS)"; (4) "locked-in syndrome"; (5) "akinetic mutism"; and (6) "minimally responsive." Descriptive information and behaviorally based definitions of each term follow. Prognostic information also is included, whenever possible. Recommendations pertain only to adult survivors of severe brain injury.

COMA

General Description

Coma is a specific neurobehavioral diagnostic term that denotes unarousability (with absence of sleep/wake cycles on electroencephalogram (EEG) and loss of the capacity for environmental interaction.[5] The neuropathologic substrate typically consists of severe, diffuse bihemispheric lesions and/or brain stem injury.[5] When injury is localized to the brain stem (eg, hemorrhage), coma results from disruption

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This official Position Paper of the American Congress of Rehabilitation Medicine was developed by the Committee on the Minimally Responsive Patient of the ACRM's Head Injury Special Interest Group. It was adopted by ACRM's Board of Governors on July 25, 1994. It has not been peer reviewed by the Editorial Board of the *Archives of Physical Medicine and Rehabilitation*. Correspondence commenting on this Position Paper should be directed to the chair of the ACRM's Committee on the Minimally Responsive Patient.

This article reflects the position of the Committee on the Minimally Responsive Patient of the American Congress of Rehabilitation Medicine—Head Injury Interdisciplinary Special Interest Group. This position has not been adopted by the American Academy of Physical Medicine and Rehabilitation.

Committee members who wrote the paper were Joseph T. Giacino, PhD, Chair; Nathan D. Zasler, MD; John Whyte, MD, PhD; Douglas I. Katz, MD; Mel Glen, MD; and Michael Andary, MD.

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of the reticular activating system usually involving the upper two thirds of the brain stem.[5]

Neurobehavioral Criteria

1. The patient's eyes do not open either spontaneously *or* to external stimulation; and
2. The patient does not follow any commands; and
3. The patient does not mouth or utter recognizable words; and
4. The patient does not demonstrate intentional movement (may show reflexive movement such as posturing, withdrawal from pain; or involuntary smiling); and
5. The patient cannot *sustain* visual pursuit movements of the eyes through a 45° arc in any direction when the eyes are held open manually; and
6. The above criteria are not secondary to use of paralytic agents.

NOTE: A Glasgow Coma Scale score of 8 or less has traditionally been considered the standard for objectively establishing the diagnosis of coma. GCS scores of 8 or less do not always correspond to the clinical definition of coma. For example, brain-injured patients with concomitant high cervical lesions may present with spontaneous eye opening (E4), flaccid limbs (M1), and inappropriate words (V3) yielding a total GCS score of 8. Although a numerical grading system may be a practical means of tracking progress for prognostic or research purposes, it is not sufficient for determining an accurate clinical diagnosis nor should it be used in isolation to establish return of consciousness.

VEGETATIVE STATE (VS)

General Description

Few patients remain in coma (ie, eyes closed, no evidence of wakefulness) for more than 4 weeks.[5] Patients who show no signs of consciousness after their eyes open usually fit the criteria for VS. The vegetative state always follows an initial period of coma after traumatic injury to the brain but may be observed in the absence of coma in dementing and metabolic disorders. VS is a specific neurobehavioral diagnostic term that indicates complete loss of the ability to interact with the environment despite the capacity for spontaneous or stimulus-induced arousal.[5,6] Behavioral responses consist of reflexive reactions only. Sleep/wake cycles may be present on EEG, and subcortical reflexes are partially or fully preserved. Vegetative (ie, autonomic) functions may no longer require artificial support. No specific neuropathologic correlates exist; however, the VS is frequently observed in patients who manifest severe bihemispheric pathology with relative preservation of brain stem structures.[5,7] The diagnosis requires serial clinical evaluation.

Neurobehavioral Criteria

1. The patient's eyes open spontaneously or after stimulation; and
2. Criteria 2, 3, 4, 5, and 6 under coma are met.

NOTE: Patients who are in VS may show spontaneous roving eye movements and may be responsive to optokinetic stimulation on full field confrontation but are incapable of visual tracking.

PERSISTENT VEGETATIVE STATE (PVS)

General Description

PVS is a prognostic term that has been used to refer to a chronic condition in which basic arousal (ie, wakefulness) and life-sustaining functions (eg, respiration, blood pressure) are generally intact despite the absence of behavioral signs of meaningful environmental interaction.[6,8] The term "persistent" indicates that the patient has remained in the VS for a prolonged period of time. However, there is considerable disagreement about the length of time required to designate the VS "persistent." The American Academy of Neurology (AAN) has recently adopted the position that the VS should be termed persistent at 1 month postinjury and that it can be considered permanent after 3 months following nontraumatic injuries and after 12 months after traumatic injuries.[9]

However, adoption of this nomenclature presents a number of potential problems. First, given the negative prognostic bias inherent in PVS, application of this term at 1 month postinjury could significantly reduce the likelihood of referral for rehabilitation services for patients who may well benefit from them. This contention is supported by recent published evidence demonstrating the influence of prognosis on recommendations for treatment.[10,11] Second, Choi et al[12] recently described the course of recovery of 71 patients who were vegetative at 3 months and found that 52% recovered consciousness by 12 months postinjury. Further, the Committee believes that introducing the concept of PVS is misleading because it implies that the condition is absolutely refractory to current treatment, and therefore, irreversible. The literature indicates that confident predictions of recovery from PVS remain elusive because reliable neurologic markers presaging recovery or failure to recover have not yet been identified.[13-15] There are also several published accounts of recovery from PVS that have occurred beyond the time frames recommended for permanence by the AAN.[16,17] The question of recovery of consciousness relates to probability. Assignation of the term PVS denotes 100% certainty, and the existing body of scientific knowledge does not support this level of confidence. Acceptance of this term could result in a decrease in longitudinal research on this population, which is already lacking.

Regarding the neuropathologic substrate of PVS, conventional belief has held that this condition is typically secondary to extensive, diffuse cortical involvement with well-preserved subcortical structures. Recently, bilateral thalamic lesions, in association with relative preservation of the cortex, have been implicated in the pathogenesis of PVS.[18]

Although the committee agrees with the AAN that the likelihood of recovery from the VS 3 months or more after nontraumatic injuries, and after 12 months following trauma, is poor, the committee does not believe that use of descriptors such as "persistent" and "permanent" clarify either the diagnosis or prognosis of the patient in the VS. In fact, these modifiers may further complicate accurate use of the term VS. The terms "persistent" and PVS should be avoided; the committee advocates simply specifying the

length of time the VS persists. Consequently, there are no specific neurobehavioral criteria.

LOCKED-IN SYNDROME (LIS)

General Description

Locked-in syndrome is a specific neurobehavioral diagnosis that refers to patients who are alert, cognitively aware of their environment, and capable of communication but cannot move or speak.[5] There are different subclassifications of LIS that relate to the extent of motor and verbal impairment ranging from complete to partial.[19] The hallmark signs of quadraplegia and aphonia are secondary to disruption of the corticospinal and corticobulbar tracts, respectively. The neuropathologic substrate usually involves lesions of the ventral pons.[5]

Neurobehavioral Criteria

1. Eye opening is well sustained (bilateral ptosis should be ruled out as a complicating factor in patients who do not open their eyes but demonstrate eye movement to command when the eyes are opened manually); and
2. Basic cognitive abilities are evident on examination; and
3. There is clinical evidence of severe hypophonia or aphonia; and
4. There is clinical evidence of quadriparesis or quadriplegia; and
5. The primary mode of communication is through vertical or lateral eye movement or blinking of the upper eyelid.

MINIMALLY RESPONSIVE (MIN-R)

General Description

"Minimally responsive (Min-R)" is a descriptive term that refers to patients who are no longer comatose or vegetative but remain severely disabled. The Min-R patient falls in the low end of the "severe disability" outcome category according to the criteria for the Glasgow Outcome Scale.[20] A large percentage of other patients properly classified as severely disabled routinely demonstrate cognitively mediated behavior. Traditionally, patients diagnosed as comatose or vegetative have been grouped under the general heading of Min-R. *This term should be reserved for use with those patients whose responses are inconsistent but indicative of meaningful interaction with the environment.*

The capacity for environmental interaction is evident on observation or is elicitable through testing. Meaningful responses are characteristically inconsistent and often dependent on external stimulation. Any instance of comprehensible verbalization, even in the absence of any other meaningful responses, would qualify the patient as Min-R. Although not directly studied, the characteristic neuropathologic substrate is probably similar to that found in PVS (ie, bilateral, diffuse cortical damage). Patients who have been in a prolonged VS often evolve into the Min-R state in which the capacity for meaningful behavior has been regained to some degree.

Neurobehavioral Criteria

This term is applied only when there is clear evidence of the following:

1. A *meaningful* behavioral response has occurred after a specific command, question, or environmental prompt (eg, attempt to shake examiner's outstretched hand). The response is considered to be unequivocally meaningful by the observer; or
2. When the evidence for meaningful responsiveness is equivocal, the response can be shown to occur *significantly* less often when the specific command, question, or prompt associated with it is not present; and
3. The response has been observed on at least one occasion during a period of formal assessment. (Formal assessment consists of regular, structured, or standardized evaluation procedures.)

NOTE: It is necessary to consider both the *frequency* and the *context* of a behavioral response to judge whether it is meaningful or purposeful. Only one or two occurrences of a particular behavior may be sufficient to consider it meaningful when the occurrence of that behavior as nonmeaningful is highly unlikely. For example, two instances of nose touching, in response to command, should be considered more meaningful than four instances of finger movement to command. The spontaneous frequency of nose touching is considerably lower than the spontaneous frequency of finger movement. Therefore, it is more likely that the few observed instances of nose touching occurred in response to command and were therefore meaningful.

AKINETIC MUTISM (AM)

General Description

Akinetic mutism (AM) is a neurobehavioral condition that is characterized by severely diminished neurologic drive or intention.[5] It represents the end point on a continuum in which movement and speech are markedly deficient. However, spontaneous visual tracking is *always* intact. Although the absence of visual tracking excludes the diagnosis of AM, it does not exclude use of the term "minimally responsive." AM can be considered a subcategory of the minimally responsive state because meaningful responses are typically inconsistent but can usually be elicited after application of sensory or pharmacologic stimulation. The underlying impairment appears to involve deficient initiation or activation of behavior and cognition.

The term "abulia" denotes a form of this disorder that is of lesser severity,[20] although there are no objective standards for differentiating it from AM. In most cases of AM, a minimal degree of movement and/or speech is elicitable, depending on the nature and intensity of stimulation provided. Neuropathologically, the condition is associated with bilateral mesencephalic, cingulate, third ventricle, and basal or mesial frontal lesions.[5,21] Knowledge of the underlying pathologic substrate may be particularly helpful in identifying patients who are minimally responsive secondary to AM. Although there are no published group outcome studies on patients with AM, clinical experience suggests that outcomes in AM patients are less favorable than those of other

minimally responsive subgroups, especially when AM persists beyond 3 months postinjury.

Neurobehavioral Criteria

1. Eye opening is well maintained and occurs in association with spontaneous visual tracking of environmental stimuli; and
2. Little to no spontaneous speech or movement is discernible; and
3. Command following and verbalization are elicitable but occur infrequently; and
4. The low frequency of movement and speech cannot be attributed to neuromuscular disturbance (eg, spasticity, hypotonus) or arousal disorder (eg, obtundation) as is typically noted in the minimally responsive state.

NOTE: There are a number of treatable medical conditions (eg, obstructive hydrocephalus, craniopharyngioma) that may cause akinesia and mutism. It is important to recognize that, in these cases, AM may be reversible with appropriate treatment.

DISCUSSION

There are several potential benefits to adopting uniform definitions of terms commonly used to describe patients with severe alterations in consciousness. First, given the prognostic implications associated with the diagnostic and descriptive terms discussed, it is imperative that clinicians' use of nomenclature be accurate and consistent in order to ensure appropriate treatment and disposition planning. The importance of establishing a diagnosis with a high degree of specificity has never been greater than in the current climate of a declining health care dollar. Patients have unwillingly been thrust into competition among themselves for appropriation of reimbursed services. Clearly, misapplication of the term PVS, for example, could result in misguided decisions to delay or withhold rehabilitative treatment in patients who may actually be able to benefit from it.

Second, there is the risk that inappropriate treatments may be administered as a result of misdiagnosis because interventions are often diagnostically driven. For example, use of sensory stimulation for a patient with locked-in syndrome (mistakenly diagnosed as vegetative) would be ill advised and possibly even contraindicated.

Finally, researchers investigating outcome prediction and treatment efficacy have become acutely aware of the problems associated with comparison of findings across studies. In some studies, there is very little description of the subjects' clinical characteristics other than provision of the diagnostic label (eg, "subjects were 16 comatose patients"). Other studies provide a diagnostic label incompatible with the clinical presentation. (eg, "The patient was a 56-year-old man who was comatose . . . The patient blinked his eyes infrequently and was reported to have squeezed a hand placed in his hand after verbal directions to do so."[22]) These discrepancies often pose insurmountable problems when attempts are made to compare the results of treatment interventions across studies. This is particularly true of studies evaluating the effectiveness of sensory stimulation and other interventions designed to promote neurobehavioral responsiveness.

The adoption of uniform definitions for nomenclature should be considered a necessary, albeit insufficient, step in advancing the treatment and scientific study of patients with severe alterations in level of consciousness. In practical terms, this appears to be a prerequisite step in the ongoing clinical decision-making process that often influences the patient's recovery course and affects the ultimate outcome. To this end, a collaborative venture between organizations within rehabilitation and neurology has recently been undertaken.[23] The purpose of this joint initiative is to develop a consensus statement on nomenclature and definitions pertinent to the comatose, vegetative, and Min-R patient. It is anticipated that this process will eventually result in the development and dissemination of practice parameters for assessment and treatment of this population. It is hoped that other organizations involved in caring for the severely brain-injured patient (eg, neurosurgery) will join and support this effort.

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